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A Lower Temperature FDM 3D Printing for the Manufacture of Patient-Specific Immediate Release Tablets

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ABSTRACT

Purpose. The fabrication of a ready-to-use immediate release tablets *via* 3D printing provides a powerful tool to on-demand individualization of dosage form. This work aims to adapt a widely used pharmaceutical grade polymer, polyvinylpyrrolidone (PVP), for instant on-demand production of immediate release tablets *via* FDM 3D printing.

Methods. Dipyridamole or theophylline loaded filaments were produced via processing a physical mixture of API (10%) and PVP in the presence of plasticizer through hot-melt extrusion (HME). Computer software was utilized to design a caplet-shaped tablet. The surface morphology of the printed tablet was assessed using scanning electron microscopy (SEM). The physical form of drug and its integrity following an FDM 3D printing were assessed using x-ray powder diffractometry (XRPD), thermal analysis and HPLC. *In vitro* drug release studies for all 3D printed tablets were conducted in a USP II dissolution apparatus.

Results. Bridging 3D printing process with HME in the presence of a thermostable filler, talc, enabled the fabrication immediate release tablets at temperatures as low as 110°C. The integrity of two models drugs was maintained following HME and FDM 3D printing. XRPD indicated that a portion of the loaded theophylline remained crystalline in the tablet. The fabricated tablets demonstrated excellent mechanical properties, acceptable in-batch variability and an immediate *in vitro* release pattern.

Conclusions. Combining the advantages of PVP as an impeding polymer with FDM 3D printing at low temperatures, this approach holds a potential in expanding the spectrum of drugs that could be used in FDM 3D printing for on demand manufacturing of individualised dosage forms.

KEYWORDS: FDM; fused filament fabrication; HME; patient-specific; immediate release.

ABBREVIATIONS

API	active pharmaceutical ingredient
CAD	computer aided design
DSC	differential scanning calorimetry
FDM	Fused Deposition Modelling
HME	hot melt extrusion
HPLC	high performance liquid chromatography
PLA	polylactic acid
PVA	Poly(vinyl alcohol)
PVP	polyvinylpyrrolidone
SEM	scanning electron microscopy
T _g	glass transition temperature
T _m	melting point
TGA	thermal gravimetric analysis
XRPD	X-ray powder diffractometry

INTRODUCTION

3D printing established roots in various disciplines from arts and engineering to implants and regenerative medicine (1, 2). As yet the exploitation of 3D printing for pharmaceutical applications is still at its infancy. However, with the emergence of the first FDA approved 3D printed tablet, Spritam (3), the momentum of this technology is on track to potentially change many means of production for oral dosage forms.

The absence of large array of commercially available API combinations and strengths remains the most frequent problem facing compounding pharmacies today (4). Traditional tableting methods require multiple processing stages, costly facilities and experienced personnel, thus rendering tablet manufacturing impractical when dose modification for one or small group of patients is required. By contrast, 3D printing, not only circumvent these challenges of conventional tableting, but also offers means of fabricating medicines at the point of dispensing (5). Amongst the different explored 3D printing technologies, fused deposition modelling (FDM) shows significant promise in low-cost dose fabrication (6). This stems up from the fact that FDM printers are available today at low cost and capable of producing 3D objects with a high accuracy and without post-printing steps (7).

Fused deposition modelling (FDM) involves passing a filament based on thermoplastic polymer through a hot nozzle, where temperature is elevated above its glass transition temperature (T_g). The extruded material is deposited layer by layer to form an object, where solidification occurs in less than a second. The potential of FDM 3D printers has been explored in the incorporation of different API molecules through their loading into commercially available PVA filaments (7-9). These previous attempts, however, displayed several limitations such as the use of non-pharmaceutical grade ingredients and limited drug loading (9, 10). Previous reports suggested the need for using high temperatures [220 °C (8), 210 °C (9) and 250 °C (7)] when PVA based dosage forms were fabricated using FDM 3D printers. Moreover, several examples of PLA printed structures employed a temperature range of 180-210 °C (11-13).

Despite the advancement in FDM 3D printing, the array of polymers currently exploited for FDM 3D printing remain limited. The employed polymers for FDM printing in oral drug delivery were restricted to the extended release polymers such as PVA (6-8) and PLA (14). The major limitation of FDM 3D printing renders it unsuitable for the

production of immediate release tablets, which count for approximately 70% of all oral dosage forms (15, 16). In rare example, our group reported the fabrication of immediate release tablet based on positively charged methacrylic polymers (17). Polyvinylpyrrolidone (PVP) is known to have a growing pharmaceutical applications with solubility enhancing abilities (18-20). It is of great interest to adapt this water soluble polymer to fabricate tablet with immediate release profile. In this current work, we explored the feasibility of employing FDM 3D printing to encompass this important polymer in the pharmaceutical field. We have used temperature in this work, up to the authors knowledge, is the lowest to have been explored in constructing drug delivery dosage forms, hence broadening the spectra of materials that could be used with FDM.

MATERIALS AND METHODS

Materials

Theophylline (melting point 270 °C) (21) was purchased from Acros Organics. Polyvinylpyrrolidone (PVP, MW 40,000) and dipyridamole (melting point 165 °C) (22) were purchased from Sigma-Aldrich (UK). Talc was ordered from Fluka Analytical (UK). Triethyl citrate was purchased from Sigma-Aldrich (Dorset, UK) and Scotch blue painter's tape 50 mm was supplied by 3M (Bracknell, UK).

Preparation of filaments using HME

For the preparation of the API-free filaments a Thermo Scientific HAAKE MiniCTW hot melt extruder (Karlsruhe, Germany) was utilised. An optimised ratio of a powder mixture constituting of the polymer (PVP), plasticizer (TEC), filler (talc) and API (theophylline or dipyridamole) at (50, 12.5, 27.5 and 10%wt) respectively, was gradually added to the HME and allowed to mix for 5 min at 100 °C to allow homogenous distribution of the molten mass. Afterwards, extrusion took place at 90 °C at a torque of 0.4 Nm.

Tablet design and printing

Tablets in this study were designed in a caplet shape using an Autodesk® 3ds Max® Design 2012 software version 14.0 (Autodesk, Inc., USA). The templates design was then imported to the 3D printer's software in a stereolithography (.stl) file format. For the printing of tablets, pre-prepared filaments were fed into a commercial FDM 3D

printer equipped with 1.75 mm nozzle size and MakerWare software Version 2.4.0.17 (Makerbot Industries, LLC., USA). Tablets were printed using modified settings of the software as described earlier in our previous work (23). Tablets were printed using modified settings of the software as follows: type of printer: Replicator 2X; type of filament: PLA; resolution: standard; temperature of building plate: 40 °C; speed of extruder 90 mm/s while extruding and 150 mm/s while traveling; infill: 100%; height of the layer: 200 µm and nozzle temperature 110 °C. The design was printed without supports or raftsto avoid the need for post-printing finishing step. In order to improve caplet's adhesion to the building plate, a blue Scotch Painter's Tape was applied to the plate's surface.

Thermal analysis

For modulated temperature differential scanning calorimetry (MTDSC) analysis, a differential scanning calorimeter (DSC) Q2000 (TA Instruments, Elstree, Hertfordshire, UK) with a heating rate of 2 °C/min was employed. Each sample was subjected to a heat-cool-heat scan in order to measure and exclude the effect of moisture contents on filament plasticity. A modulated scan was applied using an amplitude of 0.212 °C and a period of 40 sec was used, scanning from -70 to 200 °C. Analysis was carried out under a purge of nitrogen (50 mL/min). The data was analysed using a TA 2000 analysis software. TA pin-holed lid and 40 µL aluminium pans and were filled with approximately 5 mg sample. All measurements were carried out in triplicates.

For TGA analysis, printed tablets, raw materials as well as extruded filaments were measured using a TGA Q5000 (TA Instruments, Hertfordshire, UK). Samples (10 mg) were added to an aluminium pan without lid. Samples were then heated from 25 °C to 500 °C at a heating rate of 10 °C/min. All measurements were carried out in triplicates.

X-ray Powder diffractometry (XPRD)

A powder X-ray diffractometer, D2 Phaser with Lynxeye (Bruker, Germany) was used to assess the physical form of APIs in PVP, PVP:TEC filament, API-free and API-loaded filaments, and 3D printed tablets. Samples were scanned from 2Theta (2θ)= 5° to 50° using 0.01° step width and a 1 second time count. The divergence slit was 1 mm and the scatter slit 0.6 mm. The wavelength of the X-ray was 0.154 nm using Cu

source and a voltage of 30 kV. Filament emission was 10 mA using a scan type coupled with a two theta/theta scintillation counter over 30 min.

Characterisation of the tablets properties

Tablets in this study were characterised for; weight variation, drug content, friability, hardness and disintegration time. For determination of weight uniformity, 20 tablets were randomly selected and weighed individually using a digital analytical balance Ohaus® (Discovery DV215CD). The average weights of the tablets was measured and the percentage deviation from the mean was then determined.

The crushing strength of 10 tablets was measured using a TBH 220 D (Erweka GmbH, Heusenstamm, Germany). The friability of the 3D printed tablets was determined using an Erweka Friability Tester TAR 10 (Erweka GmbH, Heusenstamm, Germany). Twenty tablets were randomly selected, weighed and tested at a rotation of 25 rpm for 4 min. Tablets were then collected, dusted and reweighed. The differences in weight were calculated and displayed as a percentage of the original sample weight.

In order to determine the disintegration time for the 3D printed tablets, an Erweka ZT 220 Disintegration tester (Erweka GmbH, Heusenstamm, Germany) was utilised. Six tablets were randomly selected and individually placed in the 6 cylinders of the basket rack assembly. The tablets in the cylinders were then covered with discs and the basket rack was immersed into a beaker containing 750 mL of 0.1 M HCl at 37 ± 0.5 °C. The time required for all tablets to leave the mesh was then visually assessed.

Determination of drug content

In order to examine the effect of HME and FDM 3D printing on the integrity of drug, API-loaded filaments and 3D printed tablets were analysed for drug content prior and following HME as well as in the 3D printed tablets. Samples (dipyridamole loaded filaments or tablets) were accurately weighed and placed in a 500 mL of 1:1 water:acetonitrile mixture for 2 h under sonication. The solution were filtered through 0.22 µm Millex-GP syringe filters (Merck Millipore, USA) and prepared for HPLC analysis.

Dipyridamole contents in relevant samples were assessed using an Agilent UV-HPLC 1260 series (Agilent Technologies, Inc., Germany) equipped with XTerra RP 18 column (150 x 4.6 mm, 5µm particle size) (Waters, Ireland) at temperature 40°C. The

mobile phase (60:40 phosphate buffer pH 6.8: acetonitrile) was employed at a flow rate 1 mL/min and dipyridamole was detected at a wavelength of 282 nm. The injection volume was 10 μ L and a stop time was 10 min per sample.

For theophylline, the same UV-HPLC system and column were used as detailed above. A mobile phase constituted of 10 mM solution of ammonium acetate buffer, methanol and acetonitrile (86:7:7) was used. Analysis was carried out at a wavelength of 272 nm, temperature of 40 °C, flow rate of 1 ml/min, injection volume was 5 μ L and a run time of 7 min.

Scanning electron microscopy (SEM)

The surface morphology of the filaments and the printed tablets was examined using Quanta-200 SEM microscope at 20 kV. Samples were placed on a metallic stub and gold coated under vacuum using JFC-1200 Fine Coater (Jeol, Tokyo, Japan). Photographs of the tablets were also taken with a Canon EOS-1D Mark IV (Canon Ltd, Japan).

***In vitro* drug release studies**

In vitro drug release studies was investigated using an Erweka DT 600 dissolution tester (USP II). Three tablets were randomly selected and individually placed in the dissolution vessels each containing 900 mL of 0.1M HCL and stirred at 50 rpm and 37 \pm 0.5 °C. Four mL aliquots were manually collected using 5 mL Leur-Lok syringes at (0,5,10,15,20,25,30,40,50,60 and 70 min) time intervals and filtered through a Millex-HA 0.45- μ m filter. Each aliquot withdrawn was replaced with 4 mL of 0.1M HCl. The absorbance of the samples were finally measured using a UV spectrophotometer (Bibby Scientific Ltd, UK) at 282 and 272 nm for dipyridamole and theophylline respectively.

Statistical analysis

One-way ANOVA was employed using SPSS Software (22.0.0.2) to analyse the results. Differences in results above probability level ($p > 0.05$) was considered not significant whilst; ($p < 0.001$) were considered very significant and between $p = 0.01$ and 0.05 were considered significant.

RESULTS AND DISCUSSION

Fig. 1 illustrates different step used in the preparation of tablets by combining HME and FDM 3D printing. API, polymer and other filler were physically mixed and processed via HME to produce 1.75 mm filament at 90 °C. CAD software was used to produce a capsule-shaped tablet that was printed *via* a benchtop FDM 3D printer.

PVP is frequently used in HME to enhance the dissolution pattern of poorly soluble molecules (24-28). TGA thermographs (Figs. 2A-B) revealed a significant mass loss of PVP filaments around 100 °C due to dehydration of the PVP filaments. A second mass loss was also apparent at 400 °C indicating the degradation of PVP. Also the plasticiser TEC degrades at temperatures >200 °C (Figs. 2A-B). This renders it unsuitable for FDM 3D printing under the recommended printing temperature of 200-220 °C, thus highlighting the importance of lowering the temperature during the process of 3D printing to suit a variety of APIs and pharmaceutical excipients. The thermal stability of dipyrindamole (29) and theophylline (30) were in agreement with previous reports and both APIs were stable at temperatures <200 °C.

When PVP filament (no filler) were used as a feed for 3D printer, it was not possible to fabricate a structure *via* FDM 3D printing process due to poor flow from the hot nozzle of printer and the formation of collapsed structure (data not shown). In order to formulate a stable structure and allow rapid solidification of the filament from the hot nozzle of the 3D printer, a thermostable filler, talc (melting points being >1500 °C), was added to the composition of the filament. The latter did not degrade at the temperature range utilised in this study (31).

DSC thermographs, at the first heat-scan, all displayed a large endothermal event in the range of 50-110 °C due to polymer dehydration (Fig. 3). This might be related to the hygroscopic nature of PVP, where electronegative groups of the carbonyl in pyrrolidone structure are able to form hydrogen bonds with water (32). Therefore, a modulated heat-scan was utilized to assess this event-complex. In order to assess the impact of water on glass transition temperature (T_g), a heat-cool-heat scan was employed.

The reversing heat flow of the first heat-scan indicated that the T_g of PVP filament (plasticised with TEC) to be in the range of 19-35 °C. This T_g is significantly lower than expected from Gordon-Taylor equation (T_g =82.3 °C) and is related to the plasticising effect of water. On the other hand, the second heat-scan indicated a significantly higher T_g value of 93 °C (in comparison to the T_g of first heat-scan, $p<0.05$), confirming that moisture has an impact on the plasticity of PVP. Such a plasticizing effect of moisture on PVP was previously reported (33, 34).

The addition of talc did not show any significant effect on the thermal behaviour of PVP as noted in the first and second heat-scans. The addition of dipyridamole and theophylline shifted the T_g of the filament in the second scan from 93 °C to 73 and 69 °C respectively. Such depression in the T_g indicates a plasticizing effect of dipyridamole and theophylline. Similar findings have been reported earlier for other API-PVP blends (35).

The XRPD patterns of dipyridamole loaded filament and tablets (Fig.4) showed the absence of peaks at (2 θ)= 10.13, 17.89, 18.91, 20.42, 20.98, 23.65, 26.12, 28.49, 30.45° (36), indicating no crystalline presence in the PVP matrices. XRPD spectra for theophylline alone elucidated diffraction peaks at (2 θ) =7, 12, 14 and 24° analogous to previous findings (23, 37). However, the presence of some peaks at (2 θ) =12 and 7° indicated that a percentage of theophylline remained in the crystalline form.

In order to examine the effect of hot melt extrusion and 3D printing on the APIs, drug content analysis in the HME extruded filaments prior to 3D printing as well as in the 3D printed tablets was carried out. As elucidated in Fig. 5B, the content of drug was neither affected by HME extrusion nor by 3D printing. Content uniformity was found to be 102.60 \pm 0.59% and 100.23 \pm 0.09% for dipyridamole and theophylline, respectively, in the extruded filaments. This high drug content was found to remain the same in the 3D printed tablets (101.18 \pm 3.91% and 99.56 \pm 0.48%) for dipyridamole and theophylline, respectively. In an earlier study, FDM 3D printing at (210 °C) was found to thermally degrade more than half the drug load (5-ASA) (38). Lowering the printing temperature to 110 °C against the recommended temperature by the 3D printer manufacturer (230°C)(39) favours its use for various materials, as reflected by the high drug content in this study.

Photographs and SEM images showed that the structure of filament was smooth with few apparent gaps or voids (Figs. 1E and 5A). Fabricated tablets were constructed from overlaid layers of filament with an approximate height of 200 μm . This thickness can be increased to 400 μm or decreased into 100 μm per layer, as required, *via* adjusting the resolution of the slicing engine of the printer (23). The potential of utilising FDM 3D printing in modifying the dose to suit patient's individual needs by controlling the volume of the printed drug delivery system has also been demonstrated (7, 23).

The 3D printed tablets were evaluated for weight variation, dimensions, hardness and friability (Table I). The friability was reported to be 0% for all the formulation and the crushing strength required to deform or break the tablets was high >350 N. These values clearly demonstrates the superiority of FDM 3D printing over other 3D printed technologies such as extrusion-based (40) and powder-based 3D printing (41, 42) in terms of producing mechanically strong tablets. The generation of ready-to-use tablets at the end of the printing process without any need for finishing or drying step is another instrumental advantage of FDM 3D printing where individualised dosage forms are instantly fabricated on demand.

The disintegration time of 3D printed tablets was found to be <15 min for all tested tablets (Table I). The applicability of utilising the polymer PVP as an immediate release polymer was also demonstrated through the *in vitro* dissolution of the drugs from the 3D printed tablets. As elucidated in dissolution data (Fig. 5c), more than 85% of dipyridamole and theophylline were released within the first 30 min. This confirms the suitability of PVP as a hydrophilic carrier for engineering immediate release 3D printed dosage forms (43).

In summary, by lowering the temperature of FDM 3D printing process using a hydrophilic polymer, this work reveals the potential of adapting this 3D printing technology to a wider spectrum of drug molecules and to commonly used immediate release dosage forms. Here, the filament-forming process is HME. However, there are a series of other kinds of filament-forming methods such as wet spinning, dry spinning and electrospinning. (44, 45) This work also provides a concept about the combined usage of advanced technologies for creating novel solid dosage forms.

CONCLUSION

By combining FDM with HME, it was possible to fabricate 3D printed tablets with immediate release properties based on PVP and talc as a matrix former and a thermostable filler. The tablets were suitable to make two model drugs and achieved immediate release properties. Tablets showed excellent mechanical properties and acceptable in-batch variability. To the authors' knowledge, this is the first report of employing PVP in FDM 3D printing and a rare example of employing the process to produce immediate release tablets. The reported approach can be employed to fabricate patient-tailored tablets at relatively lower temperature (110 °C) and using pharmaceutically approved and solubility enhancing polymer. This work confirms the possibility of expanding the use of FDM 3D printing to a wider range of temperatures for on-demand fabrication of immediate release products.

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Fig. 2 TGA Thermal degradation profiles of TEC, PVP, PVP:TEC filament, API-free and API loaded filaments, and 3D printed tablets for (A) theophylline and (B) dipyrindamole.

Fig. 3 Reversing DSC thermographs of PVP, PVP:TEC filament, API-free and API-loaded filaments, and 3D printed tablets for dipyrindamole (A1 First heat-scan and A2 second heat-scan) and theophylline (B1 First heat-scan and B2 second heat-scan).

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Table I Weight uniformity, API contents, friability, crushing strength, disintegration time and dimensions of PVP based tablets (n=3 \pm STD).

Drug	Weight Uniformity \pm SD (mg)	Drug content \pm SD (%)	Friability (%)	Crushing strength (N)	Disintegration time (min)	Tablet Dimensions (Length X Width X Height)		
						L \pm SD (mm)	W \pm SD (mm)	H \pm SD (mm)
Dipyridamole	121.68 \pm 9.28	101.18 \pm 3.91	0	432.67	10	9.23 \pm 0.15	3.86 \pm 0.09	3.80 \pm 0.12
Theophylline	111.01 \pm 5.30	99.56 \pm 0.48	0	379.00	13	9.43 \pm 0.07	3.65 \pm 0.02	3.54 \pm 0.08

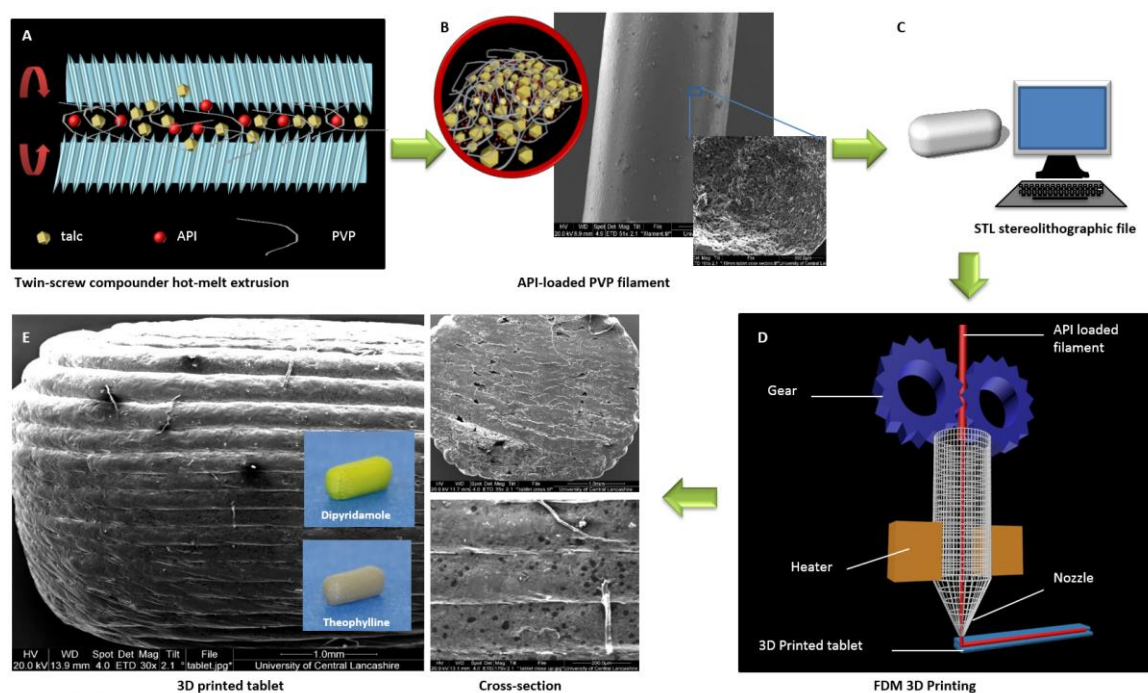


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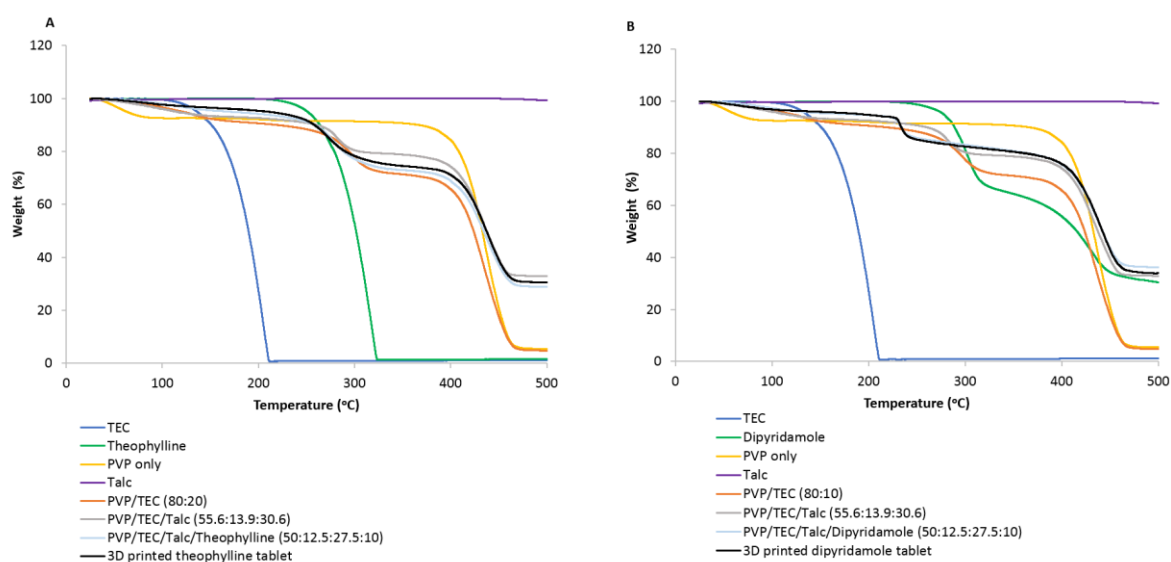


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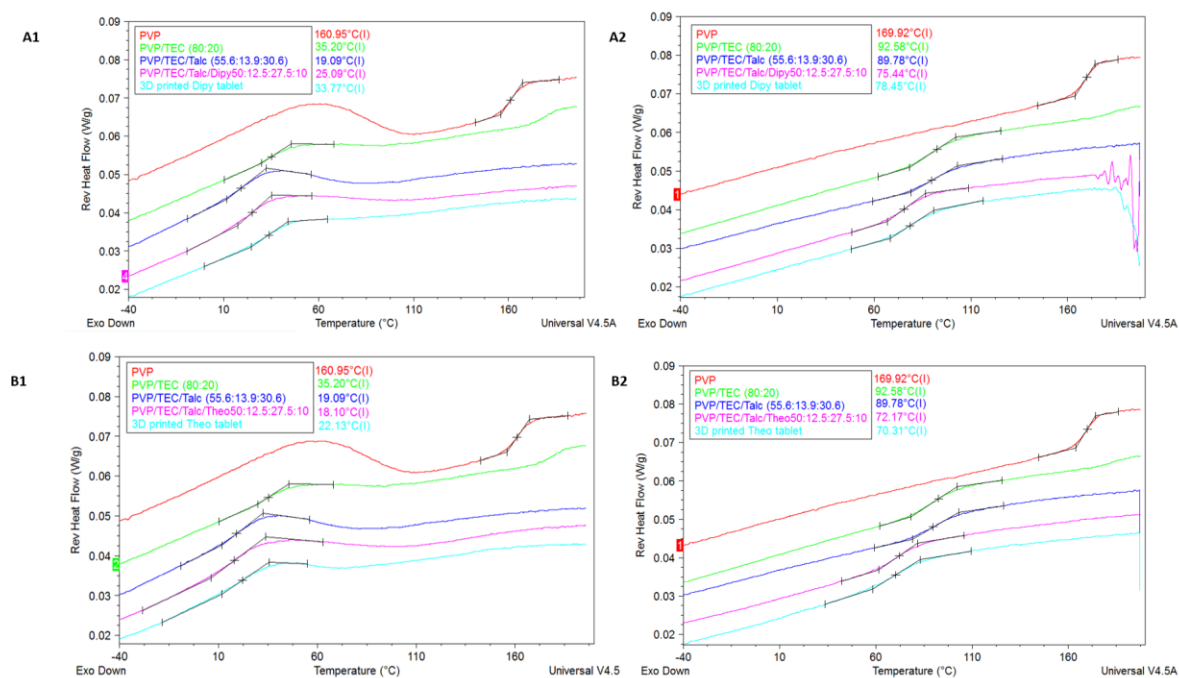


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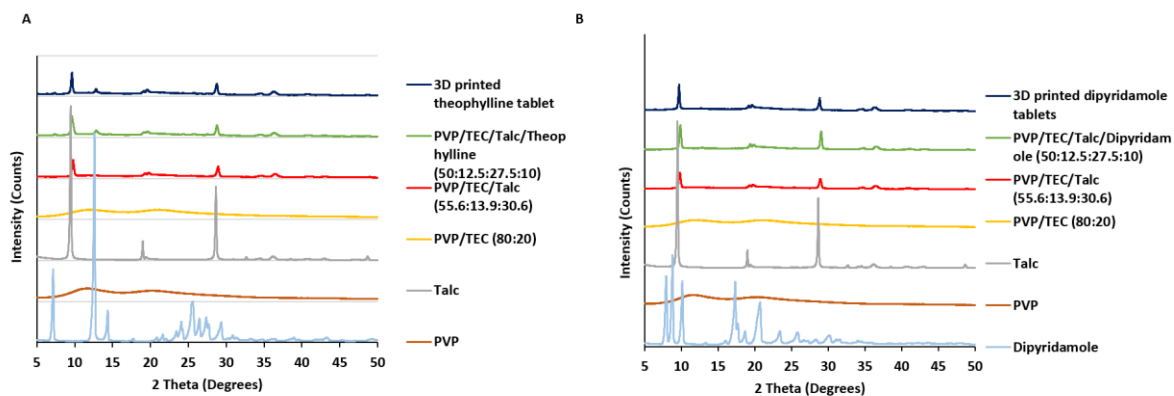


Fig. 4 XRPD patterns of PVP, PVP:TEC filament, API-free and API-loaded filaments, and 3D printed tablets for theophylline (**A**) and dipyrizidamole (**B**).

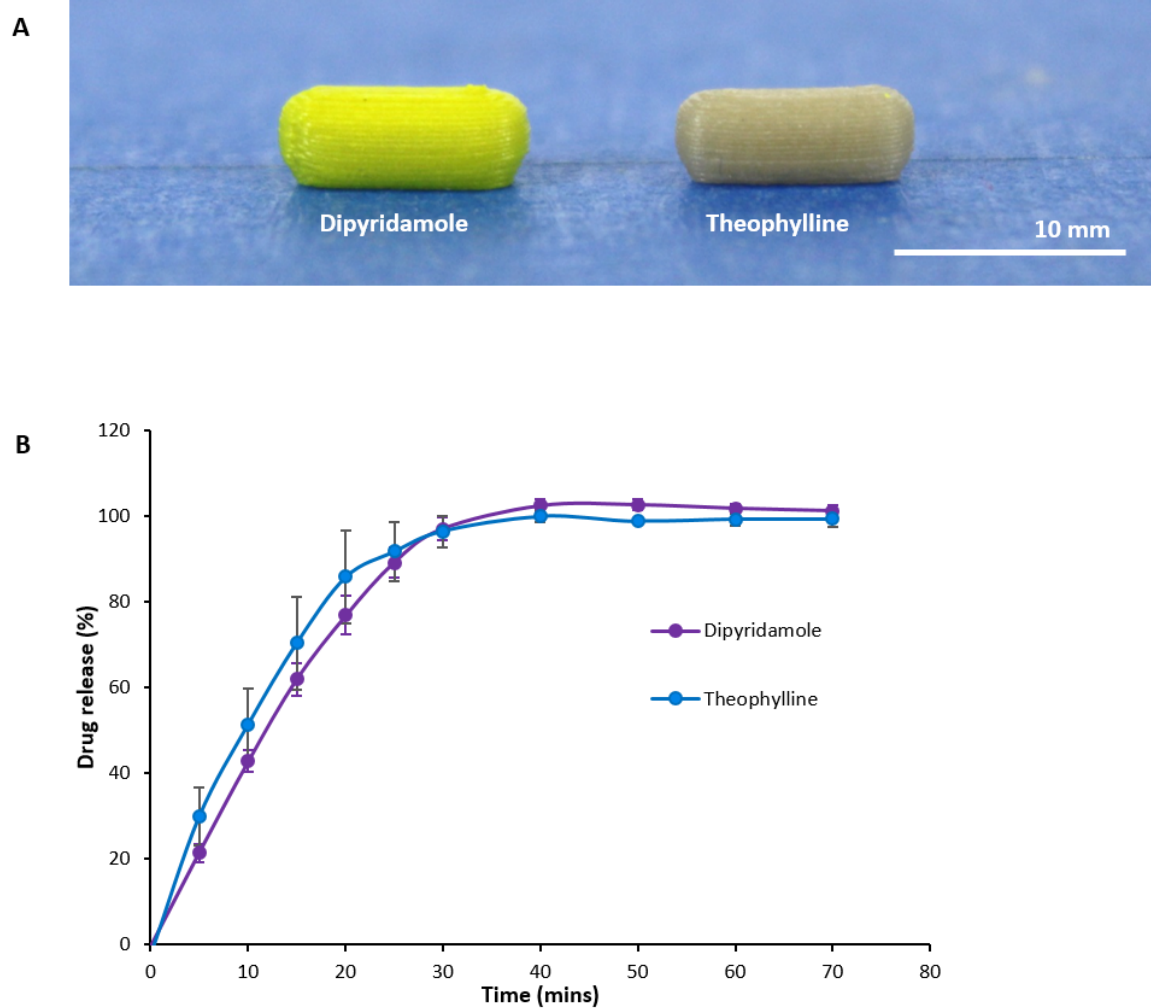


Fig. 5 (A) Photographs of 3D printed API-loaded tablets, (B) Drug contents before and after HME process and following FDM 3D printing, (C) *In vitro* dissolution profile of theophylline and dipyridamole from PVP based 3D printed tablets using USP II dissolution apparatus.

REFERENCES

1. Chung P, Heller JA, Etemadi M, Ottoson PE, Liu JA, Rand L, Roy S. Rapid and low-cost prototyping of medical devices using 3D printed molds for liquid injection molding. *Journal of visualized experiments : JoVE*. 2014(88):e51745.
2. Dombroski CE, Balsdon ME, Froats A. The use of a low cost 3D scanning and printing tool in the manufacture of custom-made foot orthoses: a preliminary study. *BMC research notes*. 2014;7:443.
3. Aprecia. Zipdose® technology. 12/3/2015. Available from: <https://aprecia.com/zipdose-platform/zipdose-technology.php>.
4. McLean S, Sheikh A, Cresswell K, Nurmatov U, Mukherjee M, Hemmi A, Pagliari C. The Impact of Telehealthcare on the Quality and Safety of Care: A Systematic Overview. *Plos One*. 2013;8(8).
5. Sanderson K. 3D printing: the future of manufacturing medicine? *Pharm J*. 2015;7865.
6. Goyanes A, Robles Martinez P, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. *International journal of pharmaceutics*. 2015;494(2):657-663.
7. Skowrya J, Pietrzak K, Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *European Journal of Pharmaceutical Sciences*. 2015;68:11-17.
8. Goyanes A, Buanz ABM, Basit AW, Gaisford S. Fused-filament 3D printing (3DP) for fabrication of tablets. *International Journal of Pharmaceutics*. 2014;476(1-2):88-92.
9. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosaliclate (4-ASA and 5-ASA) tablets. *Eur J Pharm Biopharm*. 2015;89:157-162.
10. Goyanes A, Chang H, Sedough D, Hatton GB, Wang J, Buanz A, Gaisford S, Basit AW. Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing. *Int J Pharm*. 2015;496(2):414-420.
11. Boetker J, Water JJ, Aho J, Arnfast L, Bohr A, Rantanen J. Modifying release characteristics from 3D printed drug-eluting products. *Eur J Pharm Sci*. 2016.
12. Rosenzweig DH, Carelli E, Steffen T, Jarzem P, Haglund L. 3D-Printed ABS and PLA Scaffolds for Cartilage and Nucleus Pulposus Tissue Regeneration. *Int J Mol Sci*. 2015;16(7):15118-15135.
13. Senatov FS, Niaza KV, Zadorozhnyy MY, Maksimkin AV, Kaloshkin SD, Estrin YZ. Mechanical properties and shape memory effect of 3D-printed PLA-based porous scaffolds. *J Mech Behav Biomed Mater*. 2016;57:139-148.
14. Sandler N, Salmela I, Fallarero A, Rosling A, Khajeheian M, Kolakovic R, Genina N, Nyman J, Vuorela P. Towards fabrication of 3D printed medical devices to prevent biofilm formation. *International Journal of Pharmaceutics*. 2014;459(1–2):62-64.
15. Marketsandmarkets. Drug delivery technology market. 15/10/2015. Available from: <http://www.marketsandmarkets.com/Market-Reports/drug-delivery-technologies-market-1085.html?gclid=CIXRuMT5osQCF6WtAodmiUAZg>.
16. GBIResearch. Oral drug delivery market report. 16/11/2015. Available from: http://www.contractpharma.com/issues/2012-06/view_features/oral-drug-delivery-market-report/.
17. Pietrzak K, Isreb A, Alhnan MA. A flexible-dose dispenser for immediate and extended release 3D printed tablets. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV*. 2015.
18. Knopp MM, Olesen NE, Holm P, Langguth P, Holm R, Rades T. Influence of Polymer Molecular Weight on Drug–polymer Solubility: A Comparison between Experimentally Determined Solubility in PVP and Prediction Derived from Solubility in Monomer. *Journal of Pharmaceutical Sciences*. 2015;104(9):2905-2912.

19. Shah J, Vasanti S, Anroop B, Vyas H. Enhancement of dissolution rate of valdecoxib by solid dispersions technique with PVP K 30 & PEG 4000: preparation and in vitro evaluation. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*. 2008;63(1):69-75.
20. Sharma A, Jain CP. Preparation and characterization of solid dispersions of carvedilol with PVP K30. *Research in Pharmaceutical Sciences*. 2010;5(1):49-56.
21. SIGMA-ALDRICH. Theophylline melting point standard. 2016 16/06. Available from: <http://www.sigmaaldrich.com/catalog/product/sial/phr1151?lang=en®ion=GB>.
22. SIGMA-ALDRICH. Dipyridamole. 2016 16/06. Available from: <http://www.sigmaaldrich.com/catalog/product/sigma/d9766?lang=en®ion=GB>.
23. Pietrzak K, Isreb A, Alhnan MA. A flexible-dose dispenser for immediate and extended release 3D printed tablets. *Eur J Pharm Biopharm*. 2015;96:380-387.
24. Agrawal AM, Dudhedia MS, Patel AD, Raikes MS. Characterization and performance assessment of solid dispersions prepared by hot melt extrusion and spray drying process. *Int J Pharm*. 2013;457(1):71-81.
25. Alsulays BB, Park JB, Alshehri SM, Morott JT, Alshahrani SM, Tiwari RV, Alshetaili AS, Majumdar S, Langley N, Kolter K, Gryczke A, Repka MA. Influence of Molecular Weight of Carriers and Processing Parameters on the Extrudability, Drug Release, and Stability of Fenofibrate Formulations Processed by Hot-Melt Extrusion. *J Drug Deliv Sci Technol*. 2015;29:189-198.
26. Agrawal A, Dudhedia M, Deng W, Shepard K, Zhong L, Povilaitis E, Zimny E. Development of Tablet Formulation of Amorphous Solid Dispersions Prepared by Hot Melt Extrusion Using Quality by Design Approach. *AAPS PharmSciTech*. 2016;17(1):214-232.
27. LaFontaine JS, Prasad LK, Brough C, Miller DA, McGinity JW, Williams RO, 3rd. Thermal Processing of PVP- and HPMC-Based Amorphous Solid Dispersions. *AAPS PharmSciTech*. 2016;17(1):120-132.
28. Martinez-Marcos L, Lamprou DA, McBurney RT, Halbert GW. A novel hot-melt extrusion formulation of albendazole for increasing dissolution properties. *Int J Pharm*. 2016;499(1-2):175-185.
29. Alexander V. Gerasimov MAZ, Valery V. Gorbachuk, Liana S. Usmanova. Increasing the solubility of dipyridamole using polyethylene glycols. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2014;6(9):244-247.
30. Silva Oliveira M, Miguel Agostinho SC, Guzzi Plepis AMd, Tabak M. On the Thermal Decomposition of Dipyridamole: Thermogravimetric, Differential Scanning Calorimetric and Spectroscopic Studies. *Spectroscopy Letters*. 2006;39(2):145-161.
31. Enderle JD, Bronzino JD, Blanchard SM. *Introduction to Biomedical Engineering*: Elsevier Academic Press; 2005.
32. Verdonck E, Schaap K, Thomas LC. A discussion of the principles and applications of Modulated Temperature DSC (MTDSC). *International Journal of Pharmaceutics*. 1999;192(1):3-20.
33. Szakonyi G, Zelkó R. The effect of water on the solid state characteristics of pharmaceutical excipients: Molecular mechanisms, measurement techniques, and quality aspects of final dosage form. *International Journal of Pharmaceutical Investigation*. 2012;2(1):18-25.
34. Lai MC, Hageman MJ, Schowen RL, Borchardt RT, Laird BB, Topp EM. Chemical stability of peptides in polymers. 2. Discriminating between solvent and plasticizing effects of water on peptide deamidation in poly(vinylpyrrolidone). *Journal of Pharmaceutical Sciences*. 1999;88(10):1081-1089.
35. Nair R, Nyamweya N, Gönen S, Martínez-Miranda LJ, Hoag SW. Influence of various drugs on the glass transition temperature of poly(vinylpyrrolidone): a thermodynamic and spectroscopic investigation. *International Journal of Pharmaceutics*. 2001;225(1-2):83-96.

36. Vepuri SB. Studies based on supramolecular chemistry in drug design and improvement of pharmaceutical solids. In: Department of Pharmacy: Acharya Nagarjuna University; 2014. p. 212.
37. Rasanen E, Rantanen J, Jorgensen A, Karjalainen M, Paakkari T, Yliruusi J. Novel identification of pseudopolymorphic changes of theophylline during wet granulation using near infrared spectroscopy. *J Pharm Sci.* 2001;90(3):389-396.
38. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV.* 2014.
39. Makerbot. Replicator 2X Experimental 3D Printer User Manual., http://downloads.makerbot.com/replicator2x/MakerBot_Replicator2X_UserManual_Eng.pdf In.; 2013.
40. Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. *International Journal of Pharmaceutics.* 2014;461(1–2):105-111.
41. Yu D-G, Branford-White C, Yang Y-C, Zhu L-M, Welbeck EW, Yang X-L. A novel fast disintegrating tablet fabricated by three-dimensional printing. *Drug Dev Ind Pharm.* 2009;35(12):1530-1536.
42. Katstra WE, Palazzolo RD, Rowe CW, Giritlioglu B, Teung P, Cima MJ. Oral dosage forms fabricated by Three Dimensional Printing™. *J Control Release.* 2000;66(1):1-9.
43. Liu X, Lu M, Guo Z, Huang L, Feng X, Wu C. Improving the chemical stability of amorphous solid dispersion with cocrystal technique by hot melt extrusion. *Pharm Res.* 2012;29(3):806-817.
44. Yu DG, Li XY, Wang X, Yang JH, Bligh SW, Williams GR. Nanofibers Fabricated Using Triaxial Electrospinning as Zero Order Drug Delivery Systems. *ACS Appl Mater Interfaces.* 2015;7(33):18891-18897.
45. Yang C, Yu DG, Pan D, Liu XK, Wang X, Bligh SWA, Williams GR. Electrospun pH-sensitive core shell polymer nanocomposites fabricated using a tri-axial process. *Acta Biomater.* 2016;35:77-86.